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Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Capecitabine Teva

International non-proprietary name: **capecitabine**

Procedure No. **EMEA/H/C/002362**

Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted

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List of abbreviations

2-Methyl-THF/ MeTHF	2-methyltetrahydrofuran
5-FU	5-fluorouracil
AEs	adverse events
ANOVA	analysis of variation
ASMF	active substance master file
AUC_{0-t}	area under the curve from time 0 to time t
$AUC_{0-\infty}$	area under the curve from time 0 to infinity
BSE	bovine spongiform encephalopathy
C_{max}	maximum concentration
EP or Ph. Eur.	European Pharmacopoeia
HPLC	high pressure liquid chromatography
GC	gas chromatography
ICH	International Conference on Harmonisation
IR	infra-red
LC/MS/MS	liquid chromatography followed by two rounds of mass spectrometry
LLOQ	lower level of quantification
PK	pharmacokinetics
PVC/PE/PVDC	polyvinyl chloride/polyethylene/polyvinyidene chloride
RH	relative humidity
SAEs	serious adverse events
t½	half life
ThyPase	thymidine phosphorylase
t_{max}	time to maximum (plasma) concentration
TSE	transmissible spongiform encephalopathy
USP	US Pharmacopeial Convention

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Teva Pharma B.V. submitted on 4 March 2011 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Capecitabine Teva, through the centralised procedure under Article 3 (3) of Regulation (EC) No. 726/2004– 'Generic of a Centrally authorised product'. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 29 June 2010.

The application concerns a generic medicinal product as defined in Article 10(2)(b) of Directive 2001/83/EC and refers to a reference product for which a Marketing Authorisation is or has been granted in the Union on the basis of a complete dossier in accordance with Article 8(3) of Directive 2001/83/EC.

The applicant applied for the following indication:

> Capecitabine Teva is indicated for the adjuvant treatment of patients following surgery of stage III (Dukes' stage C) colon cancer (see section 5.1).
>
> Capecitabine Teva is indicated for the treatment of metastatic colorectal cancer (see section 5.1).
>
> Capecitabine Teva is indicated for first-line treatment of advanced gastric cancer in combination with a platinum based regimen (see section 5.1).
>
> Capecitabine Teva in combination with docetaxel (see section 5.1) is indicated for the treatment of patients with locally advanced or metastatic breast cancer after failure of cytotoxic chemotherapy. Previous therapy should have included an anthracycline. Capecitabine Teva is also indicated as monotherapy for the treatment of patients with locally advanced or metastatic breast cancer after failure of taxanes and an anthracycline containing chemotherapy regimen or for whom further anthracycline therapy is not indicated.

The legal basis for this application refers to:

Generic application (Article 10(1) of Directive 2001/83/EC).

The application submitted is composed of administrative information, complete quality data and bioequivalence studies with the reference medicinal product Xeloda instead of non-clinical and clinical data.

Information on paediatric requirements

Not applicable

The chosen reference product is:

■ Medicinal product which is or has been authorised in accordance with Community provisions in accordance with Community provisions in force for not less than 6/10 years in the EEA:

Product name, strength, pharmaceutical form: Xeloda 150 mg and 500 mg film-coated tablets

Marketing authorisation holder: Roche Registration Limited

Date of authorisation: 02/02/2001

Marketing authorisation granted by: Community

Community Marketing authorisation number: EU/1/00/163/001-002

■ Medicinal product authorised in the Community/Members State where the application is made or European reference medicinal product:

Product name, strength, pharmaceutical form: Xeloda 150 mg and 500 mg film-coated tablets

Marketing authorisation holder: Roche Registration Limited

Date of authorisation: 02/02/2001

Marketing authorisation granted by: Community

Community Marketing authorisation number: EU/1/00/163/001-002

■ Medicinal product which is or has been authorised in accordance with Community provisions in force and to which bioequivalence has been demonstrated by appropriate bioavailability studies:

Product name, strength, pharmaceutical form: Xeloda 150 mg and 500 mg film-coated tablets

Marketing authorisation holder: Roche Registration Limited

Date of authorisation: 02/02/2001

Marketing authorisation granted by: Community

Community Marketing authorisation numbers: EU/1/00/163/001-002

Bioavailability study numbers: 150 mg

EudraCT No: 2009-018165-13

Study No: mp15.09

500 mg

EudraCT No: 2010-018537-22

Study No: mp26.09

Scientific advice

The applicant received Scientific Advice from the CHMP on 29 May 2009 and on 19 November 2009. The Scientific Advice pertained to clinical aspects of the dossier.

Licensing status

The product was not licensed in any country at the time of submission of the application.

1.2. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP was Tomas Salmonson.

- The application was received by the EMA on 4 March 2011.
- The procedure started on 23 March 2011.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 10 June 2011.
- During the meeting on 18-21 July 2011, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 21 July 2011.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 19 August 2011.
- The Rapporteur circulated the Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 4 October 2011.
- During the CHMP meeting on 17-20 October 2011, the CHMP agreed on a List of Outstanding Issues to be addressed in writing by the applicant. The final List of Outstanding Issues was sent to the applicant on 20 October 2011.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 11 November 2011.
- The Rapporteur circulated the Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 9 December 2011.
- During the CHMP meeting on 13-16 December 2011, the CHMP agreed on a second list of outstanding issues to be addressed in writing by the applicant. The final List of Outstanding Issues was sent to the applicant on 16 December 2011.
- The applicant submitted the responses to the CHMP second List of Outstanding Issues on 13 January 2012.
- The Rapporteur circulated the Assessment Report on the applicant's responses to the second List of Outstanding Issues to all CHMP members on 25 January 2012.
- During the meeting on 13-16 February 2012, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Capecitabine Teva on 16 February 2012.

2. Scientific discussion

2.1. Introduction

Capecitabine Teva, 150 mg and 500 mg film-coated tablets is a generic application made according to Article 10(1) of Directive 2001/83/EC.

The active substance in Capecitabine Teva is capecitabine, a non-cytotoxic fluoropyrimidine carbamate, which functions as an orally administered precursor of the cytotoxic moiety 5-fluorouracil (5-FU). Capecitabine is activated via several enzymatic steps. The enzyme involved in the final conversion to 5-FU, thymidine phosphorylase (ThyPase), is found in tumour tissues, but also in normal tissues, albeit usually at lower levels. In human cancer xenograft models capecitabine demonstrated a synergistic effect in combination with docetaxel, which may be related to the upregulation of thymidine phosphorylase by docetaxel.

The efficacy and safety of capecitabine has been demonstrated in several well-controlled studies. A summary of these studies can be found in the EPAR of the reference medicinal product Xeloda.

The indication proposed for Capecitabine Teva is the same as the authorised indication for the reference medicinal product and includes treatment of colon, colorectal, gastric and breast cancer.

Given as single agent, the recommended starting dose for capecitabine in the adjuvant treatment of colon cancer, in the treatment of metastatic colorectal cancer or of locally advanced or metastatic breast cancer is 1250 mg/m^2 administered twice daily (morning and evening; equivalent to 2500 mg/m^2 total daily dose) for 14 days followed by a 7-day rest period. Adjuvant treatment in patients with stage III colon cancer is recommended for a total of 6 months.

In combination treatment in colon, colorectal and gastric cancer, the recommended starting dose of capecitabine should be reduced to 800 – 1000 mg/m2 when administered twice daily for 14 days followed by a 7-day rest period, or to 625 mg/m2 twice daily when administered continuously. The inclusion of biological agents in a combination regimen has no effect on the starting dose of capecitabine. Premedication to maintain adequate hydration and anti-emesis according to the cisplatin summary of product characteristics should be started prior to cisplatin administration for patients receiving the capecitabine plus cisplatin combination. Premedication with antiemetics according to the oxaliplatin summary of product characteristics is recommended for patients receiving the capecitabine plus oxaliplatin combination. Adjuvant treatment in patients with stage III colon cancer is recommended for a duration of 6 months.

Finally, in combination with docetaxel, the recommended starting dose of capecitabine in the treatment of metastatic breast cancer is 1250 mg/m^2 twice daily for 14 days followed by a 7-day rest period, combined with docetaxel at 75 mg/m^2 as a 1 hour intravenous infusion every 3 weeks. Pre-medication with an oral corticosteroid such as dexamethasone according to the docetaxel summary of product characteristics should be started prior to docetaxel administration for patients receiving the capecitabine plus docetaxel combination.

Capecitabine tablets should be swallowed with water within 30 minutes after a meal. Treatment should be discontinued if progressive disease or intolerable toxicity is observed. For further posology recommendations please refer to section 4.2 of the SmPC.

The proposed pack sizes are consistent with the dosage regimen and duration of use of the reference medicinal product.

2.2. Quality aspects

2.2.1. Introduction

The product is presented as film-coated tablets containing 150 mg and 500 mg of capecitabine as active substance.

Other ingredients are defined in the SPC section 6.1.

The tablets are packed in transparent PVC/PE/PVDC – Aluminium blisters in packs of 60 tablets for the 150 mg strength and 120 tablets for the 500 mg strength.

2.2.2. Active substance

The active substance of Capecitabine Teva is capecitabine, which has the chemical name: pentyl N-{1-[(2R,3R,4S,5R)-3,4-dihydroxy-5-methyloxolan-2-yl]-5-fluoro-2-oxo-1,2-dihydropyrimidin-4-yl}carbamate. It corresponds to the molecular formula $C_{15}H_{22}FN_3O_6$ and relative molecular mass of 359.49. It appears as white to off-white not hygroscopic crystalline powder which is soluble in water and very soluble in methanol.

Capecitabine has chiral properties and the molecule contains four stereogenic centers. The configuration matches with the corresponding positions 5-deoxy-β-D-ribofuranosyl. And has a specific rotation between +96.0° and +100.0° for a 1.0 % w/v solution in methanol (20º C, Sodium D line).

A physical characterization report regarding the crystal structure of capecitabine has been presented. It has been shown that, capecitabine manufactured by the active substance supplier is consistent with regard to the crystalline form. It has been further demonstrated that it is anhydrous and that no polymorphic transformation occurred under the conditions tested after slurring in different solvents or when subjected to high pressure, dry grinding and heating. No other polymorphic forms are stated to be known from the literature.

Manufacture

An ASMF has been submitted for the drug substance.
Detailed information regarding the control of starting materials, reagents and raw materials as well as the control of critical steps and intermediates is provided in the ASMF.

The synthesis process is sufficiently described in the ASMF, the choice of the starting materials has been justified, and so have been the process controls, specifications and test methods. Satisfactory information on the validation production batches, on the manufacturing process development and on the methods used in the control of the starting materials were also provided. The ASMF holder has adequately discussed the potential carry-over of all reagents, solvents and auxiliary material and their presence in the final drug substance.

Specification

The specification of the active substance as set up by the drug product manufacturer includes tests and limits for appearance (visual), identification (IR, HPLC), specific optical rotation (Ph.Eur.), water

(Ph.Eur.), residue on ignition (Ph.Eur.), heavy metals (Ph.Eur.), assay (HPLC), related substances (HPLC), residual solvents (GC), particle size distribution (laser light diffraction) and microbiological quality (Ph.Eur.). The specifications are adequate to control the quality of the active substance. The impurity limits are acceptable and there is no concern from the point of view of safety.

Batch analysis data is presented in the ASMF for three batches. All the results reported are all within proposed specifications. In addition the applicant presented batch analysis data from another five batches of capecitabine which have been used to manufacture film-coated tablets. These batches have been tested against the full set of specifications as proposed by the applicant including the results from microbiological testing and particle size analysis. All the results reported are all within proposed specifications.

Stability

Two production scale batches of capecitabine have been placed on accelerated (40°C/75% RH), intermediate (30°C/65% RH) and long term (25°C/60% RH) conditions according to ICH guidance.

The batches are packaged in double polyethylene bags placed in a carton drum. Appearance, HPLC identity, water content, assay and related substances are monitored during the stability studies.

24 months of long term, twelve months of intermediate and six months of accelerated data were reported. No significant changes in any of the parameters studied were observed and all results were within the proposed specifications under either the long term or the intermediate conditions.

Also after six months at the accelerated condition, all results for the parameters studied were within the proposed specifications.

Photostability and forced degradation studies for the drug substance demonstrated that the drug substance can be considered photo-stable in the solid state.

Based on the stability data provided the proposed re-test period is supported.

2.2.3. Finished medicinal product

Pharmaceutical development

The aim of the product development was to formulate a medicinal product essentially similar, robust, stable and bioequivalent to the reference medicinal product.
The excipients are all common for this type of dosage form and their usage can be considered justified. Also, the excipients of the tablet core are qualitatively the same as those of the original product. The stability reported studies reveal no incompatibilities between the active substance and excipients or the packaging materials.
The formulation was optimised by varying the amounts of intra- and extra granular excipients. Dissolution testing has been used as a tool to select suitable formulations showing similar dissolution profiles with the reference product. A wet granulation method was selected in order to prevent segregation and avoid homogeneity problem and the final formula and process were optimised to achieve acceptable compressibility and desirable dissolution profiles.
The dissolution method used for routine testing has been properly developed and sufficiently justified. It has been shown to be reasonably discriminatory versus manufacturing process changes and is considered acceptable as a routine dissolution test method. Dissolution profiles between test and

reference for both strengths have been provided. Bioequivalence studies against both strengths of reference product of the final selected formulation have been performed for the generic products. Since bioequivalence has been shown for both strengths of test and reference, any differences of the dissolution profiles are considered of no concern. The active substance particle size specifications have been set in line with the particle size measured for the drug substance used for the bioequivalence batches.
Comparative impurity profiles between the generic and reference products have been presented.
The tablets are packaged in PVC/PE/PVDC-aluminium blisters. Leakage testing is performed on the blister package.

Adventitious agents

Except lactose anhydrous, no TSE risk materials are used in the manufacture of the finished product. It has been confirmed by the manufacturer of the lactose that it is derived from milk, sourced from healthy animals in the same conditions as milk collected for human consumption and is prepared in accordance with the relevant requirements laid down in Note for Guidance EMEA/410/01, rev2. Appropriate TSE/BSE free declarations were provided.

Manufacture of the product

The manufacturing method is considered a standard method comprising blending, wet granulation, drying, blending and compression. Standard equipment is used. The two strengths are manufactured by similar but slightly different processes. The in-process specifications has been satisfactorily justified. The manufacturing process has been validated on two pilot scale batches of the respective strength using commercial scale equipment. A validation scheme for the first three commercial batches for each strength has been agreed. The actual commercial batch size has been defined. All registration batches, which are described in the dossier, are validated.

Product specification

The finished product release and shelf-life specifications includes tests and limits for appearance (visually), identification of drug substance (HPLC, IR), disintegration (Ph.Eur.), average mass (Ph.Eur.), uniformity of dosage units (Ph.Eur.), dissolution (Ph.Eur.), and microbial purity (Ph.Eur.), degradation products (HPLC), assay (HPLC), and microbiological quality (Ph.Eur.).
The proposed limits for the impurities are considered to have been toxicologically qualified and are considered acceptable. Batch analysis data have been presented for two pilot scale batches of finished product of both strengths (four batches in total including the bioequivalence batches) packaged in blisters. All results reported were within proposed specifications and indicate that the process is under control, confirming consistency and uniformity of manufacture.

Stability of the product

Primary stability studies according to ICH guidance have been initiated on two pilot scale batches of the respective 150 mg and 500 mg strengths of tablets. The batches are packaged in the proposed Al-PVC/PE/PVDC blister package and have been stored under long term 25°C/60% RH, intermediate 30°C/75% RH and accelerated 40°C/75% RH conditions. The same methods are used, as for the release testing.

The following data were reported: up to 18 months of long term, up to twelve months of intermediate and six months of accelerated data.
In the long term condition capecitabine tablets packaged in the proposed blister package comply with all specifications for the parameters monitored in the study. Only a slight increase in one impurity (metabolite) and total impurities are seen. In the intermediate condition the batches comply with the specifications and only a small increase in one impurity (metabolite) was seen.
In the accelerated conditions the batches comply with all the specifications after 6 months. The only exception is an increase for two impurities which stay however within the set limits. Some out of specification results were observed for a third impurity (metabolite), the total impurities, dissolution and assay in some of the tested batches. These results from the accelerated storage condition show that a temperature storage precaution is necessary for the finished product.
A photostability study according to ICH guidance has been performed on one batch of each strength. The film-coated tablets are not considered light-sensitive and no special storage precaution in this respect is considered necessary.
Based on the overall results an acceptable shelf-life and storage conditions have been established.

2.2.4. Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in the clinic.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.2.6. Recommendation(s) for future quality development

Not applicable

2.3. Non- clinical aspects

2.3.1. Introduction

A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. The non-clinical aspects of the SmPC are in line with the SmPC of the reference product. The impurity profile is discussed below and was considered acceptable.

Therefore, the CHMP agreed that no further non-clinical studies were required.

2.3.2. Ecotoxicity/environmental risk assessment

No Environmental Risk Assessment was submitted. This was justified by the applicant as the introduction of Capecitabine Teva manufactured by Teva Pharma B.V. is considered unlikely to result in any significant increase in the combined sales volumes for all capecitabine containing products and the exposure of the environment to the active substance. Thus, the ERA is expected to be similar and not increased.

2.3.3. Discussion on non-clinical aspects

For the composition of the products under consideration, capecitabine Teva 150/500 mg tablets, the following excipients were used: lactose (anhydrous), microcrystalline cellulose, hypromellose, sodium croscarmellose, magnesium stearate, opadry y-7000 white, ferri oxidum flavum and ferri oxidum rubrum. These excipients are used in the manufacturing of oral pharmaceutical products and are all EP listed.

With respect to the synthetic process and the impurity profile of the capecitabine raw material used for the product under consideration, impurities were tested and limited according to USP specifications. The applicant claimed that the specifications used to control the quality of capecitabine active substance of the drug substance manufacturer were in accordance with the USP monograph of capecitabine with additional tests on Particle Size, Residual Solvents and Microbial Purity. In the manufacturing process residual solvents were tested and their limits were according to current ICH guidelines for all except 2-methyltetrahydrofuran (2-Methyl-THF or MeTHF), for which the applicant proposed a limit and also provided relevant toxicological data from the literature. In conclusion, the limit for MeTHF was considered acceptable from the toxicological point of view and the amount of MeTHF in this formulation of capecitabine was considered toxicologically justified.

There were three drug-related impurities namely, compound A (USP) 5'-deoxy-5-fluorocytidine; compound B (USP) 5'-deoxy-5-fluorouridine and compound C (USP) 2'3'-O-carbonyl-5'-deoxy-5-fluoro-N4-(pentyloxycarbonyl) cytidine (USP) .The limits of these impurities were higher than recommended by the Note for Guidance on Impurities in New Drug Product /CPMP/ICH/2738/99) with a qualification threshold of 0.15% for drug products with a maximum daily dose of > 2g which is the case for capecitabine tablets (maximum daily dose for normal body surface area person is 4.3 g).

Impurities A and B are metabolites of capecitabine and hence were considered qualified for that reason. For the compound C, due to the nature of the indication and treatment regimen (given in a limited number of days/cycles) and known pharmacological/toxicological profile of the parent drug, the proposed level as set by the shelf-life could be considered qualified. This is in line with guidance in ICH S9, which is the relevant guideline to consider for a product used for the present indication.

2.3.4. Conclusion on the non-clinical aspects

In conclusion, the non-clinical overview presented by the applicant is largely based on published scientific literature which is acceptable since capecitabine is a well known active substance. There are no objections to the approval of Capecitabine Teva from a non-clinical point of view. The SmPC of Capecitabine Teva is similar to that of the originator product Xeloda and it is therefore acceptable.

2.4. Clinical aspects

2.4.1. Introduction

This is an application for film-coated tablets containing capecitabine. To support the marketing authorisation application the applicant conducted 2 bioequivalence studies with cross-over design under fed conditions. These studies were the pivotal studies for the assessment.

The applicant provided a clinical overview outlining the pharmacokinetics and pharmacodynamics as well as efficacy and safety of capecitabine based on published literature. The SmPC is in line with the SmPC of the reference product.

No formal scientific advice by the CHMP was given for this medicinal product. For the clinical assessment, the Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev.1) in its current version is of particular relevance.

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant

Exemption

Not applicable as bioequivalence studies have been conducted with both strengths applied for.

Clinical studies

To support the application, the applicant has submitted two bioequivalence studies; one study with the 150 mg tablet (study 130/09-06.CE) and one with the 500 mg tablet (study 005/10-06.CE).

2.4.2. Pharmacokinetics

Study 130/09-06.CE

Methods

Study design

This was a multicentre, single-dose, randomised, open label, two-sequence, two-treatment, four-period, replicate crossover, bioavailability study in 70 male and female patients under fed conditions.

The clinical part of the study was conducted between 13 April 2010 and 13 September 2010

The analytical part of the study was conducted between 25 June and 5 July 2010, between 1 and 14 September 2010 and between 16 and 24 November 2010 Patients received capecitabine at 1250 mg/m^2 every 12 h for 14 days in accordance with the standard dosage recommendations for XELODA.. For pharmacokinetic evaluation, the morning dose of Days 1, 2, 8, and 9, was replaced by a fixed dose of thirteen 150 mg tablets (total dose 1950 mg) from the assigned investigational medical product in each period according to the randomization schedule. The evening dose on Days 1, 2, 8, and 9 was of the commercially available product that the patient normally consumed during this treatment cycle. Since only patients receiving a daily dose of 3600 mg - 4600 mg were included into the study, the total daily dose on Days 1, 2, 8, and 9 could deviate from the normal daily dose by no more than 8.2 %.

Prior to dose administration in the morning of Days 1, 2, 8, and 9, all patients were served a standardised high-fat, high-calorie breakfast, after a minimum 10 h fasting period. The study medications were administered orally with 240 ml of water. Blood-samples were collected pre-dose and at 0.33, 0.67, 1.0, 1.33, 1.67, 2.0, 2.33, 2.67, 3.0, 4.0, 6.0 and 8.0 hours after drug administration.

Test and reference products

Capecitabine, 150 mg tablets, distributed by TEVA, Haarlem, The Netherlands (3B909038S, expiry date: 10 September 2010, assayed content: 100.7%) has been compared to Xeloda, 150 mg tablets, manufactured by Roche Pharma AG, Germany (batch No. U6013B01, expiry date: April 2012, assayed content: 96.4%).

Population studied

A total of 70 adult male and female (39 female, 31 male) patients with a diagnosis of colon cancer, metastatic colorectal cancer, locally advanced breast cancer or metastatic breast cancer, aged 39-83 years were enrolled. One patient was withdrawn before administration of the second dose of the reference treatment due to an adverse event (severe nausea); she had received one administration of the reference and one of the test treatment. All patients receiving at least one administration of the test and one of the reference product were included in the pharmacokinetic analysis.

Analytical methods

Plasma concentrations of capecitabine were determined with an LC/MS/MS method.

Pre-study validation

Specificity was shown employing six independent sources of human plasma. Sensitivity at the limit of quantification, 50 ng/ml, was shown. Satisfactory between- and within-run accuracy and precision was shown for low, medium and high QC sample concentrations. Linearity was demonstrated within the calibration range 50-20 000 ng/ml. Dilution integrity for a factor of 10 was demonstrated. Stability in plasma was demonstrated for 6 h at room temperature, for 32 weeks at – 20 °C and – 80 °C and over three freeze-thaw cycles.

Within-study validation

Satisfactory method performance during study sample analysis was demonstrated. Appropriate batch acceptance criteria were used. Repeated analysis was adequately justified. Long-term stability for a period covering the time from first sample collection until last sample analysis (21 weeks) was demonstrated. LLOQ was below 1/20 of average C_{max}.

Pharmacokinetic variables

Pharmacokinetic variables were calculated using conventional non-compartmental methods. The pharmacokinetic variables included C_{max}, AUC_{0-t}, $AUC_{0-\infty}$, t_{max}, t½ and extrapolated AUC.

Statistical methods

The statistical analysis was performed on log-transformed AUC_{0-t} and C_{max} using ANOVA. The protocol stated that bioequivalence was to be concluded if the 90% confidence intervals for the test/reference ratio of the population geometric means fell within 80.00-125.00% for AUC_{0-t} and C_{max}.

Results

Table 1. Pharmacokinetic parameters for capecitabine 13x150 mg (non-transformed values)

Pharmacokinetic parameter	Test		Reference	
	arithmetic mean	SD	arithmetic mean	SD
$AUC_{(0-t)}$	9096	5567	9305	5984
$AUC_{(0-\infty)}$	9488	5539	9647	6068
C_{max}	6290	5244	6482	6147
T_{max}*	1.39	0.33-2.67	1.45	0.33-6.01
AUC_{0-t}	area under the plasma concentration-time curve from time zero to t hours (ng*h/ml)			
$AUC_{0-\infty}$	area under the plasma concentration-time curve from time zero to infinity (ng*h/ml)			
C_{max}	maximum plasma concentration (ng/ml)			
T_{max}	time for maximum concentration (* median, range) (h)			

Table 2. Statistical analysis for <analyte> (ln-transformed values)

Pharmacokinetic parameter	Geometric Mean Ratio Test/Reference	Confidence Intervals	CV%*
$AUC_{(0-t)}$	98.34	95.36-101.41	15.36
C_{max}	101.44	93.16-110.45	44.35
* estimated from the Residual Mean Squares			

The extrapolated AUC was less than 20% in all but two subjects after administration of test and in three subjects after administration of reference product.

No pre-dose concentrations were detected. A few subjects reached t_{max} at the first sampling point (six and two subjects after administration of test replicate 1 and 2 respectively and three and three subjects after administration of reference replicate 1 and 2 respectively).

Safety data

130 AEs were observed in 34 of the 70 patients (48.6%). The observed AEs were mainly mild (59) or moderate (57) in intensity and 14 events were severe. A causal relationship to the drug was considered reasonably possible in 80 of the 130 AEs. Gastrointestinal disorders were the most frequently observed AEs, reported in 24 patients (34.3%). The most frequent AEs were nausea (13 events), dyspepsia (11 events), diarrhoea (7 events), constipation (7 events), flatulence (5 events), abdominal pain (5 events) and vomiting (3 events).

No deaths and no serious adverse events occurred in this trial. One patient was withdrawn prematurely from the study due to severe nausea.

At the end of the study, 100 AEs were resolved, 7 were resolving and 21 AEs were not resolved. 1 AE worsened during the study and for 1 AE the outcome is unknown.

Study 005/10-06.CE

Methods

Study design

This was a multicentre, single-dose, randomised, open label, two-sequence, two-treatment, four-period, replicate crossover, bioavailability study in 72 male and female patients under fed conditions.

The clinical part of the study was conducted between 19 July 2010 and 26 October 2010

The analytical part of the study was conducted between 14 and 23 September 2010 and between 24 November and 13 December 2010

Patients received capecitabine at 1250 mg/m^2 every 12 h for 14 days in accordance with the standard dosage recommendations for Xeloda. For pharmacokinetic evaluation, the morning dose of Days 1, 2, 8, and 9, was replaced by a fixed dose of four 500 mg tablets (total dose 2000 mg) from the assigned investigational medical product in each period according to the randomisation schedule. The evening dose on Days 1, 2, 8, and 9 was of the commercially available product that the patient normally consumed during this treatment cycle. Since only patients receiving a daily dose of 3600 mg - 4600 mg were included into the study, the total daily dose on Days 1, 2, 8, and 9 could deviate from the normal daily dose by no more than 6.5%.

Prior to dose administration in the morning of Days 1, 2, 8, and 9, all patients were served a standardised high-fat, high-calorie breakfast, after a minimum 10 h fasting period. The study medications were administered orally with 240 ml of water. Blood-samples were collected pre-dose and at 0.33, 0.67, 1.0, 1.33, 1.67, 2.0, 2.33, 2.67, 3.0, 4.0, 6.0 and 8.0 hours after drug administration.

Test and reference products

Capecitabine, 500 mg tablets, distributed by TEVA, Haarlem, The Netherlands (batch No. 6B910019S, expiry date: 19 October 2010, assayed content 101.3%) has been compared to Xeloda, 500 mg tablets, manufactured by Roche Pharma AG, Germany (batch No. U9390B01, expiry date: June 2012, assayed content 97.1%).

Population studied

A total of 72 adult male and female (40 female, 32 male) patients with a diagnosis of colon cancer, metastatic colorectal cancer, locally advanced breast cancer or metastatic breast cancer, aged 34-78 years were enrolled. Five patients discontinued the study prematurely. Primary reasons for discontinuation were adverse events in four patients, and non-compliance with the protocol in one patient. All patients had received at least one administration of the test and one of the reference product. In two of these patients, protocol violations were identified and the pharmacokinetic samples were destroyed without documentation. Therefore no pharmacokinetic data were available for these patients. All patients receiving at least one administration of the test and one of the reference product were included in the pharmacokinetic analysis. Altogether 70 subjects were included in the pharmacokinetic analysis.

Analytical methods

Plasma concentrations of capecitabine were determined with an LC/MS/MS method.

Pre-study validation

Specificity was shown employing six independent sources of human plasma. Sensitivity at the limit of quantification, 50 ng/ml, was shown. Satisfactory between- and within-run accuracy and precision was shown for low, medium and high QC sample concentrations. Linearity was demonstrated within the calibration range 50-20 000 ng/ml. Dilution integrity for a factor of 10 was demonstrated. Stability in plasma was demonstrated for 6 h at room temperature, for 32 weeks at – 20 °C and – 80 °C and over three freeze-thaw cycles.

Within-study validation

Satisfactory method performance during study sample analysis was demonstrated. Appropriate batch acceptance criteria were used. Repeated analysis was adequately justified. Long-term stability for a period covering the time from first sample collection until last sample analysis (21 weeks) was demonstrated. LLOQ was below 1/20 of average C_{max}.

Pharmacokinetic variables

Pharmacokinetic variables were calculated using conventional non-compartmental methods. The pharmacokinetic variables included C_{max}, AUC_{0-t}, $AUC_{0-\infty}$, t_{max}, t½ and extrapolated AUC.

Statistical methods

The statistical analysis was performed on log-transformed AUC_{0-t} and C_{max} using ANOVA. The protocol stated that bioequivalence was to be concluded if the 90% confidence intervals for the test/reference ratio of the population geometric means fell within 80.00-125.00% for AUC_{0-t} and C_{max}.

Results

Table 3. Pharmacokinetic parameters for capecitabine 4x500 mg (non-transformed values)

Pharmacokinetic parameter	Test		Reference	
	arithmetic mean	SD	arithmetic mean	SD
$AUC_{(0-t)}$	7406	3670	7139	3338
$AUC_{(0-\infty)}$	7539	3677	7366	3414
C_{max}	5777	4548	5235	3896
T_{max}*	1.16	0.33-8.00	1.63	0.33-4.00
AUC_{0-t}	area under the plasma concentration-time curve from time zero to t hours (ng*h/ml)			
$AUC_{0-\infty}$	area under the plasma concentration-time curve from time zero to infinity (ng*h/ml)			
C_{max}	maximum plasma concentration (ng/ml)			
T_{max}	time for maximum concentration (* median, range) (h)			

Table 4. Statistical analysis for <analyte> (ln-transformed values)

Pharmacokinetic parameter	Geometric Mean Ratio Test/Reference	Confidence Intervals	CV%*
$AUC_{(0-t)}$	102.46	99.02-106.02	16.06
C_{max}	108.38	100.04-117.42	41.44
* estimated from the Residual Mean Squares			

The extrapolated AUC was less than 20% in all but one subject after administration of test and in two subjects after administration of reference product.

No pre-dose concentrations were detected. A few subjects reached t_{max} at the first sampling point (three and seven subjects after administration of test replicate 1 and 2 respectively and four and three subjects after administration of reference replicate 1 and 2 respectively).

Safety data

83 AEs were observed in 25 of the 72 patients (34.7%). The observed AEs were mainly mild (39) or moderate (33) in intensity and 11 events were severe. A causal relationship to the drug was considered reasonably possible in 51 of the 83 AEs. Gastrointestinal disorders were the most frequently observed AEs, reported in 11 patients (15.3%). The most frequent AEs were vomiting (5 events), headache (4 events) and dizziness (4 events).

No deaths occurred in this trial. Four patients discontinued the study due to AEs. In two of these patients SAEs were reported.

At the end of the study, 60 AEs were resolved, 7 were resolving and 13 AEs were not resolved. 2 AEs worsened during the study and for 1 AE the outcome is unknown.

Conclusions

Based on the presented bioequivalence studies Capecitabine Teva is considered bioequivalent with Xeloda.

2.4.3. Pharmacodynamics

No new pharmacodynamic studies were presented and no such studies are required for this application.

2.4.4. Post marketing experience

No post-marketing data are available. The medicinal product has not been marketed in any country.

2.4.5. Discussion on clinical aspects

In this application no new efficacy or safety data have been submitted and none are required. The applicant has provided an acceptable review of clinical trial published in literature, describing the efficacy and safety profile of capecitabine. No new dose recommendations compared with the reference product have been made for this generic application.

Studies 130/09-06.CE and 005/10-06.CE, the two pivotal bioequivalence studies, were both multicentre, single-dose, randomised, open label, two-sequence, two-treatment, four-period, replicate crossover, bioavailability studies in male and female patients under fed conditions. There is nothing in the study reports that gives rise to any doubts regarding GCP-compliance. Three of the clinical sites are regular cancer clinics.

A single-dose bioequivalence study is adequate to demonstrate bioequivalence of an orally administered immediate-release formulation. Moreover, as the SmPC of the reference product recommends administration within 30 minutes after a meal, a study in the fed state is appropriate.

Both studies were part of the patients' regular therapy and therefore the dosage schedule had to be adjusted to fit into the regular schedule. Given the very short half-life of 0.85 h of capecitabine, the sampling period and wash-out period are considered long enough. The absorption phase is likely covered with the given sampling schedule.

Both bioequivalence studies were performed in patients, which is acceptable since capecitabine is a cytotoxic substance and not suitable for administration in healthy volunteers. Reasons for withdrawal of patients from the study were considered acceptable.

The performance of the analytical method was satisfactory.

For AUC_{0-t} and C_{max} the 90% confidence interval for the ratio of the test and reference products fell within the conventional acceptance range of 80.00-125.00%.

The statistical model used is not the one that is recommended as the primary approach for replicate designs in the Guideline on the Investigation of Bioequivalence (CPMP/QWP/EWP/1401/98 Rev. 1). What may cause the results to be different is if there are many subjects who do not provide data for all periods. Here, 69 out of 70 patients included in the analysis of pharmacokinetics completed the entire course of the study. Hence, with few subjects with missing data and, considering that the results are convincing, the method used is accepted.

It is preferable that no subjects reach t_{max} at the first sampling point. Given the short half-life of capecitabine it is however understandable that this occurs in a few patients and it is not considered to have affected the overall results.

2.4.6. Conclusions on clinical aspects

There are no objections to approval from a clinical point of view. Bioequivalence between the test and reference product has been adequately demonstrated.

2.5. Pharmacovigilance

Detailed description of the pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

Risk management plan

The CHMP did not require the applicant to submit a risk management plan because the application is based on a reference medicinal product for which no safety concerns requiring additional risk minimisation activities have been identified.

The CHMP, having considered the data submitted, was of the opinion that routine pharmacovigilance was adequate to monitor the safety of the product.

No additional risk minimisation activities were required beyond those included in the product information.

PSUR submission

The PSUR submission schedule should follow the PSUR schedule for the reference product, which currently is on a 3-yearly cycle. The next data lock point for the reference medicinal product is 31 October 2014.

User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

3. Benefit-risk balance

This application concerns a generic version of capecitabine film coated tablets. The reference product Xeloda is indicated for the adjuvant treatment of patients following surgery of stage III (Dukes' stage C) colon cancer.

Capecitabine is indicated for the treatment of metastatic colorectal cancer.

Capecitabine is indicated for first-line treatment of advanced gastric cancer in combination with a platinum based regimen.

Capecitabine Teva in combination with docetaxel is indicated for the treatment of patients with locally advanced or metastatic breast cancer after failure of cytotoxic chemotherapy. Previous therapy should have included an anthracycline. Capecitabine Teva is also indicated as monotherapy for the treatment of patients with locally advanced or metastatic breast cancer after failure of taxanes and an anthracycline containing chemotherapy regimen or for whom further anthracycline therapy is not indicated

No nonclinical studies have been provided for this application but an adequate summary of the available nonclinical information for the active substance was presented and considered sufficient. From a clinical perspective, this application does not contain new data on the pharmacokinetics and pharmacodynamics as well as the efficacy and safety of the active substance; the applicant's clinical overview on these clinical aspects based on information from published literature was considered sufficient.

The two bioequivalence studies form the pivotal basis with a multicentre, single-dose, randomised, open label, two-sequence, two-treatment, four-period, replicate crossover design in cancer patients under fed conditions. The design of the studies was considered adequate to evaluate the bioequivalence of this formulation and was in line with the respective European requirements. Studies in the fed state were considered appropriate, as the SmPC of the reference product recommends administration within 30 minutes after a meal. Choice of dose, sampling points, overall sampling time and wash-out periods were adequate. The analytical method was validated. Pharmacokinetic and statistical methods applied were adequate.

The test formulation of Capecitabine Teva met the protocol-defined criteria for bioequivalence when compared with Xeloda. The point estimates and their 90% confidence intervals for the parameters AUC_{0-t}, $AUC_{0-\infty}$, and C_{max} were all contained within the protocol-defined acceptance range of 80 to 125%. Bioequivalence of the two formulations was demonstrated.

A benefit/risk ratio comparable to the reference product can therefore be concluded.

The CHMP, having considered the data submitted in the application and available on the chosen reference medicinal product, is of the opinion that no additional risk minimisation activities are required beyond those included in the product information.

4. Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Capecitabine Teva in the following indication:

"Capecitabine is indicated for the adjuvant treatment of patients following surgery of stage III (Dukes' stage C) colon cancer.

Capecitabine is indicated for the treatment of metastatic colorectal cancer.

Capecitabine is indicated for first-line treatment of advanced gastric cancer in combination with a platinum based regimen.

Capecitabine Teva in combination with docetaxel is indicated for the treatment of patients with locally advanced or metastatic breast cancer after failure of cytotoxic chemotherapy. Previous therapy should have included an anthracycline. Capecitabine Teva is also indicated as monotherapy for the treatment of patients with locally advanced or metastatic breast cancer after failure of taxanes and an anthracycline containing chemotherapy regimen or for whom further anthracycline therapy is not indicated."

is favourable and therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, section 4.2).

Conditions and requirements of the Marketing Authorisation

Pharmacovigilance System

The MAH must ensure that the system of pharmacovigilance, presented in Module 1.8.1 of the marketing authorisation, is in place and functioning before and whilst the product is on the market.

Risk management system

Not applicable

PSUR cycle

The PSUR cycle for the product will follow PSURs submission schedule for the reference medicinal product.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Not applicable